米のものであり，わが国でのTIAに関する大規模な臨床研究はほとんどなかった。このような背景から，2009年に，厚生労働科学研究費補助金「一過性脳虚血発作（TIA）の診断基準の再検討，ならびにわが国の医療環境に則した適切な診断・治療システムの確立に関する研究」班（研究代表者：峰松一夫。以下，TIA研究峰松班と略す）が組織され，わが国の医療環境に即したTIA診療システムの改革，再構築が模索されている。

本稿では，現在抜本的な見直しがなされつつあるTIAの定義，原因，症候，画像診断，医療体制について，過去の研究から今後の展開までを概説する。

Ⅰ．TIAの定義

1．国外におけるTIAの定義の変遷

TIAという用語は，1958年にフィッシャー（Charles Miller Fisher）により初めて用いられたとされている[2]。フィッシャーは，「数秒から数時間，典型的には数秒から5～10分持続する発作」を脳卒中発症前の警告発作と考え，TIAと命名して詳細に報告した。そして同年，米国の脳血管障害分類（CVD-I）において，脳血管障害の主要病型の1つとしてTIAが記載された[3]。そこでは「脳梗塞を伴わない一過性脳虚血」と記載されたが，当時は梗塞巣の有無は剖検でしか判断できなかった。

1975年に改訂されたCVD-Ⅱでも「症状持続時間が24時間以内」とする定義が採用された[4]。1990年に発表されたCVD-Ⅲにもそれは受け継がれ，「24時間以内に消失する脳虚血による一過性の局所神経症状で，画像上の梗塞巣の有無は問わない」とした定義が広く用いられてきた[5]。

しかし，近年の画像診断，特に拡散強調画像（diffusion weighted image：DWI）を含めたMRIの普及に伴い，症状が1時間以上持続する例では虚血病巣が高率に認められることが報告され[6]，このような症例の扱いが問題になってきた。そこで2002年には，米国TIAワーキンググループが，「神経症状がより短期間，典型的には1時間以内に消失し，かつ画像上脳梗塞巣が認められないもの」とする新しい定義を提案し[7]，2006年の米国心臓病協会（American Heart Association：AHA）/米国脳卒中協会（American Stroke Association：ASA）ガイドラインにもこの定義が踏襲された[8]。

2009年のAHA/ASA学術声明では，TIAの診断を症状持続時間で区切ることはあまり意味がないとし（明確な持続時間に言及せず），「局所の脳，脊髄，網膜の虚血により生じる一過性神経学的機能障害で，画像上脳梗塞巣を伴っていない」ことを基準とする立場を示した[2]。画像検査ができずに脳梗塞かTIAかを確定診断できない場合は両者を区別せずに，急性神経血管症候群（acute neurovascular syndrome：ANVS）と呼ぶことも提唱された。

このように，主として米国では，症状持続時間に基づく定義から，画像診断上の組織障害の有無に基づく定義に変わりつつある。

2．わが国におけるTIAの定義の変遷と現状

わが国では，1962年の文部省総合研究班（冲中班）による脳血管障害の分類で，「脳梗塞を伴わない一過性脳虚血」が脳血管障害の一病型として記載された[9]。その後，1985年の厚生省循環器病委託研究班（田崎班）の分類で，TIAは「局所神経徴候は24時間以内（多くは1時間以内）に完全に消失するもの」と定義された[10]。1990年の同研究班（平井班）の分類では，「脳虚血による局所症状が出現するが24時間以内（多くは1時間以内）に完全に消失し，頭部CT上，責任病巣に一致する器質的病変が見られないもの」とされ，画像所見に関する定義が加えられた[11]。

TIA研究峰松班では，2009年11月に日本脳卒中学会認定研修教育病院683施設を対象としたアンケート調査を実施した[12]。その結果，約9割の施設が「症状持続時間が24時間以内」とする診断基準を用いており，画像上の梗塞巣の有無を問う，問わないはほぼ半々に分かれていることが明らかになった（Fig. 1）。

3．TIA研究峰松班によるTIAの定義

TIA研究峰松班によるTIAの定義をTable 1に示す。TIA研究峰松班では，DWIを脳梗塞かTIAかの診断のための手段ではなく，TIA例における脳卒中発症リスクを評価する最も重要な手段の1つと位置づけた。この定義を用いれば，専門医療機関のみならず画像検査のできない医療機関においてもTIAの診断が可能であり，また，DWIで虚血病巣を認める場合を「DWI陽性のTIA」として区別することにより，最近国外で用いられている組織障害の有無に基づく定義にも対応可能である。

症状持続時間を24時間以内とした理由は，①これまでのデータとの互換性を保つことと，②わが国の脳卒中専門施設の大部分が「持続時間は24時間以内」とする定義を用いていることによる。また，画像上の梗塞巣の

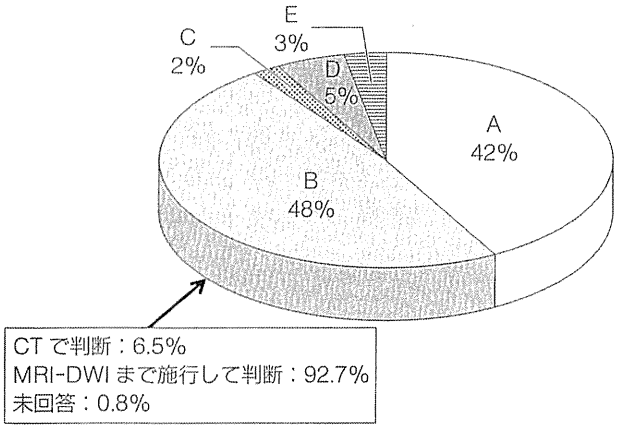

Fig. 1　わが国の脳卒中専門病院において日常診療で用いられている TIA の定義

A：神経症状持続時間が 24 時間以内で，画像上の脳梗塞巣の有無を問わない（1990 年，NINDS-CVD Ⅲ），B：神経症状持続時間が 24 時間以内で，画像上，脳梗塞巣を認めない（1990 年，平井班），C：神経症状持続時間が 1 時間以内で，画像上の脳梗塞巣の有無を問わない，D：神経症状持続時間が 1 時間以内で，画像上，脳梗塞巣を認めない（2006 年，AHA/ASA ガイドライン），E：神経症状が一過性（持続時間を問わず）で，画像上，脳梗塞巣を認めない（2009 年，AHA/ASA 声明）。

上原敏志，峰松一夫，厚生労働科学研究費補助金による「TIA の診断基準の再検討，ならびにわが国の医療環境に則した適切な診断・治療システムの確立に関する研究」班：「一過性脳虚血発作」の新展開と治療　日本脳卒中学会認定研修教育病院を対象とした一過性脳虚血発作（TIA）の診療に関するアンケート調査。脳卒中 32: 710-718, 2010 より一部改変して転載

有無を問わないとした理由は，①画像上病巣を認める例を脳梗塞，認めない例を TIA とする米国の定義では，DWI 施行の有無のみならず，DWI の施行時期が診断に大きく影響すること[13]，②DWI 病変が必ずしも不可逆的な梗塞病変を意味しないことによる。

4．急性脳血管症候群の概念

近年，急性期の TIA と脳梗塞とを包括した「急性脳血管症候群（acute cerebrovascular syndrome：ACVS）」という概念が提唱されている[14]。前述の ANVS も類似の概念である。これらの概念は，不安定狭心症と急性心筋梗塞を包括する「急性冠症候群（acute coronary syndrome：ACS）」という概念に対応する。TIA を救急疾患として捉え，脳梗塞と同様に早期診断・治療を行うことの重要性を表す用語である。

5．今後の展開

現在改訂中の ICD（International Classification of Diseases of the World Health Organization）第 11 版では，時間（24 時間）と梗塞巣の有無とを組み合わせた新しい TIA の定義が検討されている（World Stroke Organization 理事会での報告）。どのような定義に落ち着こうとも，症状持続時間（特に 24 時間以内か否か）と DWI 病巣の有無は，重要な診断根拠となることが確実であり，その両者を記録しておくことが重要である。

Table 1　TIA の診断基準（TIA 研究峰松班）

(1) 臨床症状
24 時間以内に消失する，脳または網膜の虚血による一過性の局所神経症状
(2) 画像所見
画像上の梗塞巣の有無は問わない。
＊頭部 MRI 拡散強調画像（DWI）で新鮮病巣を認める場合は「DWI 陽性の TIA」とする。

急性期の TIA と虚血性脳卒中を包括して急性脳血管症候群（acute cerebrovascular syndrome：ACVS）と呼ぶ。

Ⅱ．TIA の症候

症候の持続時間が短いため，医療者が TIA を観察できることは少ない。したがって，病歴のみから TIA か否かの判断をする必要がある。しかし，米国の救急医が TIA 以外の疾患を TIA と誤診した率は 60%と報告されており[15]，また，神経内科医の間であっても病歴のみから診断した場合の一致率は 42～86%と報告されている[16,17]。TIA 研究峰松班のアンケート調査でも，「非脳卒中専門医から TIA 疑いで紹介された患者のうち，実際に TIA である割合はどのくらいと思われますか？」との質問に対して，約 8 割の脳卒中専門施設が「50%以下」と回答した[12]。

TIA の症候（Table 2）は突然出現することが特徴であり，ほとんどが数分以内に完成する。症状が徐々に悪化する場合，症状のある部位が変化する場合は，TIA ではないことが多い[5]。症候の持続時間は約 50%が 30 分以内であり，多くは数分から数十分の持続時間である[18]。日常診療では，「箸を落とした」「言葉が一瞬出なかった」などの訴えから TIA を疑われる場合も多いが，持続時間が非常に短い（数秒以内）場合は，TIA としては非典型的である[5]。Japan Multicenter Stroke Investigator's Collaboration（J-MUSIC）でまとめられた TIA の症候は，運動麻痺が最多で（64.7%），次いで言語障害，歩行障害の順であった[19]。当院の検討では，TIA の症候が進行，変動する場合には，そうでない例よりも脳梗塞を発症する危険性が高いという結果で

Table 2　TIA の症候（NINDS Classification of CVD-III）

左頸動脈系の症候
a．運動機能異常（構音障害，右上下肢および/または顔面の脱力，[完全] 麻痺，または巧緻運動障害）
b．左眼の視力喪失（一過性黒内障），または稀に右視野の視力喪失（右同名半盲）
c．感覚症状（右上肢および/または下肢および/または顔面を含む感覚脱失または paresthesia を含むしびれ感）
d．失語（言語障害）
右頸動脈系の症候
・左頸動脈系の場合と反対側に同様な症状を呈する
・失語症は，言語に関する優位半球が右の場合のみ生じる
椎骨脳底動脈系の症候
a．運動機能異常（脱力，[完全] 麻痺，または巧緻運動障害）の組み合わせ（上肢・下肢・顔面の左右どちらか一側あるいは両側）
b．感覚症状（左右どちらか一側あるいは両側の感覚脱失，しびれ感，または paresthesia）
c．左右どちらか一側あるいは両側の同名性視野障害
d．姿勢調節障害，回転性めまい，平衡障害，複視，嚥下障害，構音障害（これらは単独では，TIA とはみなされない）
TIA としては非典型的な症候
a．椎骨動脈系の徴候を伴わない意識消失
b．強直性あるいは間代性痙攣
c．症状が身体の複数の部位に広がっていく場合
d．閃輝暗点
TIA とみなされない症候
a．身体の他の部位に広がっていく（行進性の）感覚障害
b．回転性めまいのみ
c．浮動性めまい（めまい感）のみ
d．嚥下障害のみ
e．構音障害のみ
f．複視のみ
g．尿あるいは便の失禁
h．意識レベルの変化に伴う視力障害
i．片頭痛に伴う局在症状
j．意識不鮮明（confusion）のみ
k．健忘のみ
l．転倒発作（drop attack）のみ

用語は，原則として日本神経学会用語委員会（編）『神経学用語集　改訂第3版』に従った。

Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. Stroke 21: 637-676, 1990 より転載

あり[20]，これらの有無を確認することも重要である。

III．TIA の原因

TIA から脳梗塞への進展を防止するためには，病型に対応する治療が必要であり，発症機序の観点から分類を行うことは重要である。

TIA の病態は，アテローム血栓性機序によるものが基本であり，なかでも主幹動脈，動脈硬化病変からの（微小）塞栓性が主であるが，主幹動脈の狭窄に基づく血行力学性機序による TIA も存在するとされてきた[21,22]。しかし，近年の研究結果から，TIA においても脳梗塞同様，アテローム血栓性以外の機序が少なからず関与することがわかってきた[23]。

TIA 症例が，入院加療中に脳梗塞を発症した場合の臨床病型を検討したわが国の複数の報告では，発症時脳梗塞病型の約半数がラクナ梗塞であった[24-26]。この結果は，わが国において，細動脈病変を原因とする，いわゆるラクナ型の TIA が軽視すべきでない重要な病態であることを示唆している。同時に，他の機序の TIA と比べて治療介入が難しいことを示しているのかもしれない。

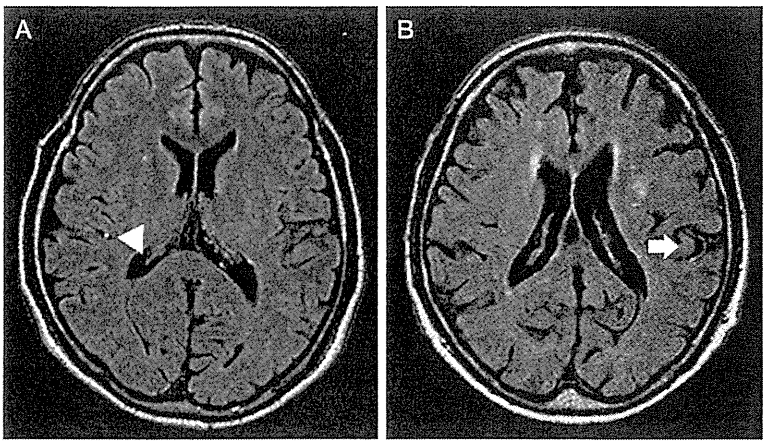

Fig. 2　TIA 患者にみられた FLAIR 画像での血管高信号（FVH）
A：シルヴィウス裂内の点状 FVH（◁）。B：シルヴィウス裂遠位の蛇行状 FVH（矢印）。
Kobayashi J, Uehara T, Toyoda K, Endo K, Ohara T, et al: Clinical significance of fluid-attenuated inversion recovery vascular hyperintensities in TIA. Stroke (in press) より転載

TIA に類似した病態として，“spectacular shrinking deficit（SSD）”が挙げられる[27]。これは，広汎な半球症候を示しながら，24 時間以内に臨床症候の劇的改善を示すものである。ただし，症候が 24 時間以上続く場合も含んでいる。心原性脳塞栓症の約 12%にみられ，血栓の分解，移動による早期の血行再開がその原因と考えられている。SSD の存在は，心原性塞栓の機序による TIA が少なくないという傍証でもある。前述の J-MUSIC 研究，当院および TIA 研究峰松班の後ろ向き研究では，TIA 患者の 17%が心房細動を有していた[19,28]。高齢化に伴い，心房細動を有する患者が増加していくことを考えると，心房細動が関与する心原性 TIA の絶対数は今後増加していく可能性がある。

Ⅳ．TIA の画像診断

24 時間以内の神経症候消失という，従来の定義による TIA 患者においても，MRI により 30～50%に虚血病巣が発見されること[24,29–32]，症状の持続時間に比例して虚血病巣が発見される率が高まること[31]，虚血病巣を有する例では脳梗塞を発症しやすいことが報告されている[2,29,30]。TIA 研究峰松班のアンケート調査では，TIA の患者に対し，全体の 97.5%の施設が MRI を必須と回答した[12]。米国やカナダでは，TIA の初期評価に MRI が用いられるのは 5～15%と報告されており[33,34]，わが国における TIA 診療は，画像診断の面においては，諸外国を大きくリードしていることがうかがえる。

最近，TIA の画像診断において，DWI のみならず，FLAIR（fluid-attenuated inversion recovery）画像での血管高信号（FLAIR vascular hyperintensity：FVH）の有用性を示す報告が散見される[35,36]。FVH は，虚血性脳血管障害でしばしば認められる所見であり，血管の閉塞や血流速度の低下に関連すると報告されている[37]。当院の検討では，発症から 24 時間以内に MRI を受けた 202 例の TIA 患者の 20%に FVH を認めた（Fig. 2）[36]。FVH は頭蓋内血管の閉塞性病変に関連して出現し，DWI で虚血病巣を認めなくとも FVH が陽性になる例も存在した。また，MRA 上の閉塞性病変と FVH の両方を有する例では 90 日以内の脳梗塞または TIA の再発が多いことも明らかになった。FLAIR を含めた他の撮像法と DWI を組み合わせることは，TIA の診断，予後予測という点で，特にわが国において今後の発展が期待される。

Ⅴ．TIA の診療体制

1．TIA の早期診断・治療の有効性

TIA および軽症脳卒中患者を対象とした英国の EXPRESS 試験では，治療開始時期などのプロトコール改訂前後での比較を行い，早期診断・治療が 90 日以内の脳卒中発症率に及ぼす影響について検討した[38]。第 1 相では，一般家庭医の診察後に専門機関である TIA クリニックを予約受診するシステムをとり，第 2 相では，直ちに TIA クリニックを受診するシステムをとった。また，治療に関しては，第 2 相でクロピドグレルやスタチン，2 剤以上の降圧薬の服用が多かった。その結果，早期診断・治療により 90 日以内の脳卒中発症リスクを 80%も低減することが示された（Fig. 3）。

また，専門家が TIA 患者を 24 時間体制で受け入れるシステム（SOS-TIA）を構築して 24 時間以内に TIA の治療を開始すれば，その後の脳卒中発症を著しく減少できることがフランスから報告された[39]。

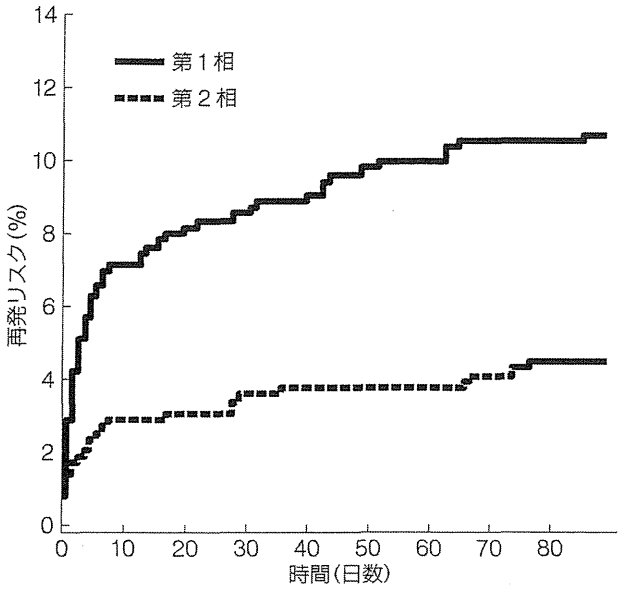

Fig. 3　EXPRESS 試験の TIA または軽症脳卒中患者全体における最初の医療機関受診後の脳卒中再発リスク
90 日目の脳卒中発症率は，第 1 相（10.3%）に比べて第 2 相（2.1%）で有意に低く（$P<0.0001$），早期診断・治療により脳卒中発症リスクが 80%低減された。第 1 相：まず一般家庭医の診察を受け，その後に専門機関である TIA クリニックを予約受診する（専門医の診断までの期間は 3 日，治療開始までの期間は 20 日）。第 2 相：直ちに TIA クリニックを受診するシステム（専門医の診断，治療開始までの期間はいずれも 1 日）。
Rothwell PM, Giles MF, Chandratheva A, et al: Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. Lancet **370**: 1432-1442, 2007 より改変して転載

Table 3　ABCD² スコア

A（Age）	60 歳以上	1 点
B（Blood pressure）	収縮期血圧 140 mmHg≧and/or 拡張期血圧≧90 mmHg	1 点
C（Clinical features）	片側脱力	2 点
	脱力を伴わない言語障害	1 点
D（Duration）	60 分以上	2 点
	10～59 分	1 点
D（Diabetes）	糖尿病あり	1 点

2 日以内の脳卒中リスクは，スコア 0～3：1.0%，スコア 4～5：4.1%，スコア 6～7：8.1%。
Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, et al: Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet **369**: 283-292, 2007 より転載

2．ABCD² スコアを用いた入院適応判断

TIA 後早期の脳卒中発症リスクは一律ではないため，高リスクの TIA 患者を効率よく正確にトリアージし，入院の適応を判断する必要がある。TIA の簡便な診断，リスク層別化，緊急度判断に用いられるスコアとして，ABCD² スコアが広く用いられている（Table 3）[40]。A（age），B（blood pressure），C（clinical features），D（duration および diabetes）の合計点が高いほど脳卒中発症リスクは高くなる。また，本スコアは，非専門医の TIA 診断精度を上げるのに有用であるとの報告もある[41]。

2009 年に発表された AHA/ASA の学術声明によると，72 時間以内に TIA のイベントがあった場合，①ABCD² スコアが 3 以上の場合，②ABCD² スコア 0～2 で，2 日以内に外来で診断的精密検査が完了できない場合，③ABCD² スコア 0～2 で，発作の原因が局在性の虚血であるという証拠がある場合は，入院させるのが妥当であるとしている[2]。また，ABCD² スコアに加えて，DWI の虚血病巣，頸動脈狭窄性病変や心房細動を認める例も脳卒中発症リスクが高いため，緊急入院させることが推奨されている。

3．わが国の TIA 医療体制の現状

1）TIA 診療における一般開業医と脳卒中専門施設間の連携

TIA 研究峰松班では，大阪北部の開業医（内科・外科 835 件，眼科 107 件，耳鼻科 86 件）を対象とした TIA に関する意識調査を行った。内科・外科を対象としたアンケート調査では，脳卒中や TIA を疑う患者が受診した際の対応について，「1 時間前に発症し，診察

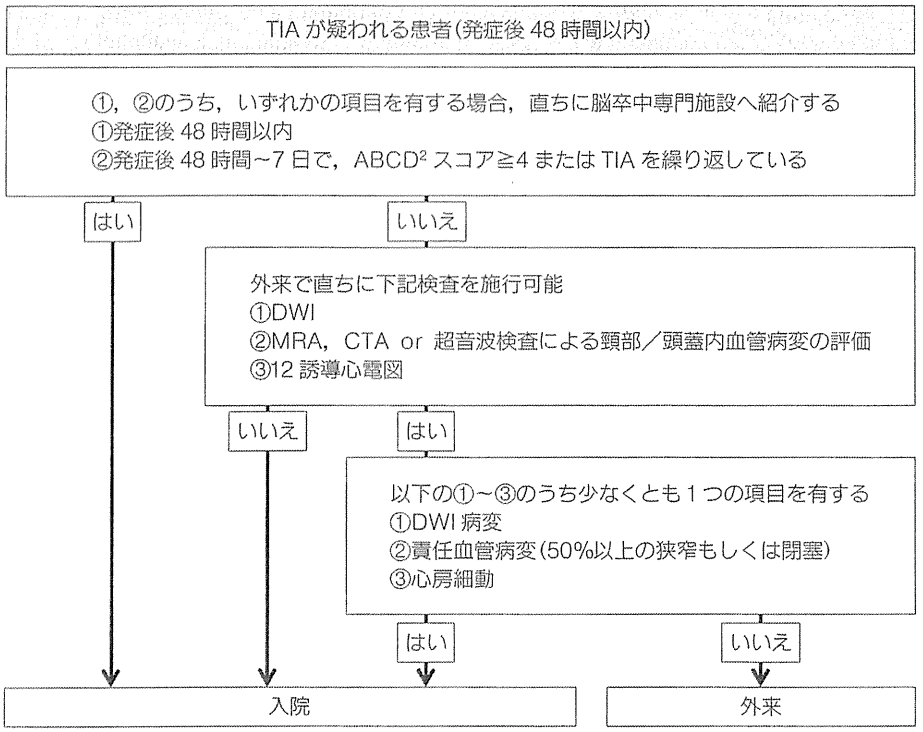

Fig. 4　わが国における TIA の初期対応に関する TIA 研究峰松班の試案
〔略語〕ABCD²：age, blood pressure, clinical features, duration と diabetes, DWI：拡散強調画像

時にも症状が持続している場合」は,「直ちに脳卒中専門病院に紹介する」との回答が 85.1%を占めていたが,「1 時間前に発症し, 診察時には症状が消失している場合」は,「直ちに脳卒中専門病院に紹介する」との回答が 42.9%に減り,「直ちにではないが脳卒中専門病院に紹介する」との回答は 36.8%にみられた。「TIA 患者を専門施設に紹介するにあたり困ることがありますか？」の質問に対して「困ることがある」との回答が 70%を占め,「TIA の診断に自信がない」「紹介する病院に困る」などの回答が多かった。

眼科, 耳鼻科を対象としたアンケート調査でも内科・外科とほぼ同様の結果が得られた。TIA 診療における開業医から脳卒中専門施設へのアクセスの難しさが明らかとなり, 気軽に相談できるシステム構築の必要性が示された。

2）わが国の脳卒中専門施設における TIA 診療の特徴

TIA 研究峰松班のアンケート調査では, 発症 24 時間以内の TIA 患者が来院した場合の入院の適応方針については, 66.2%の脳卒中専門施設が「原則として全例入院させる」と回答し,「ABCD² スコアなどの脳卒中発症予測スコアを用いて判断する」と回答したのは 7.3%のみであった[12]。実施する検査のうち, CT, MRI, MRA, 12 誘導心電図, 血液検査については大部分の施設が「必ず行う」と回答した。抗血栓療法については, 65%の施設が「原因精査を行った上で, 24 時間以内に抗血小板療法もしくは抗凝固療法を開始する」と回答した。

4．わが国における TIA の診断基準および初期対応の提案

わが国における TIA の初期対応に関する TIA 研究峰松班の試案を Fig. 4 に示す。まず, 患者・家族・開業医が相談できる電話相談窓口による一次トリアージを行い, TIA の可能性が高い例を 24 時間体制の専門施設で直ちに評価（MRI, MRA, 頸部血管超音波, 心電図など）を行う。そして, DWI で虚血病巣, 責任血管病変（頸動脈および頭蓋内動脈狭窄性病変）や心房細動を有する症例は入院加療とする。脳卒中発症予測スコアについては, ABCD² スコア 3 以上を入院の適応とする欧米のデータがそのままわが国にも当てはまるかどうかは不明であるため, 現在進行中の「外来受診した TIA 例の前向き登録研究」など今後の研究成果をもとにその活用法を検討する予定である。

おわりに

TIA研究峰松班では，既にわが国独自のTIA診療指針の初版を完成させ，近日中に公開する予定である。同研究班は，2012年から厚生労働科学研究費補助金「脳卒中高リスク群の診断及び治療による循環器疾患制圧に関する研究」班（研究代表者：峰松一夫）に引き継がれ，上述したTIA例の前向き登録研究が継続されている。また，わが国も参加する研究者主導型大規模国際共同研究（TIA registry. org）が現在進行中である[14]。これは，TIA患者を長期に追跡することにより，イベントリスク，診断・治療の実態を明らかにすることを目的としており，中間解析結果は，2013年11月に東京で行われるInternational TIA/ACVS Conferenceで発表される予定である。

TIA後早期の診断・治療は極めて重要である。欧米で考案されたTIA診療システムの有効性は証明されているものの，医療環境が大きく異なるわが国にそのまま適用することには慎重でなくてはならない。わが国における画像診断の普及などの利点を生かしつつ，脳卒中医療に携わる人材不足などの欠点を補うことができるような，独自の診断・治療システムを確立することは喫緊の課題である。

謝辞

本稿の作成にあたっては，厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）H21-循環器（生習）-一般-017「一過性脳虚血発作（TIA）の診断基準の再検討，ならびにわが国の医療環境に則した適切な診断・治療システムの確立に関する研究」，およびH24-循環器（生習）-一般-011「脳卒中高リスク群の診断及び治療による循環器疾患制圧に関する研究」の援助を得た。

ご助言をいただいた国立循環器病研究センター脳血管内科の上原敏志医長，尾原知行医長，鈴木理恵子医師，小林潤平医師に深謝する。

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Brief Review

Prevention of Hypertension and Cardiovascular Diseases

A Comparison of Lifestyle Factors in Westerners and East Asians

Yoshihiro Kokubo

Appropriate lifestyle modifications are a fundamental step to prevent hypertension, which is the strongest risk factor for cardiovascular disease (CVD).[1,2] However, the slope of the association between blood pressure (BP) and stroke is steeper among Asians than Westerners.[3,4] This result is partly explained by the higher proportion of strokes that are hemorrhagic in Asian compared with Western populations and the steeper association of BP with hemorrhagic stroke as compared with ischemic stroke.[5] The population-attributable fractions of hypertension for ischemic stroke in men and women have been reported as 40% and 36% in China, 34% and 35% in South Korea, 37% and 39% in Japan (East Asian), 15% and 44% in Australia, and 18% and 43% in New Zealand (Western), respectively.[6] These differences between Westerners and East Asians depend on both genetic (racial) and lifestyle factors.

A schema of the progression from lifestyle behaviors to the onset of stroke and coronary heart disease (CHD) is shown in the Figure. Lifestyle (modifiable) and genetic (unmodifiable) factors are key cardiovascular risk factors, especially higher BP (the primary stage of CVD prevention). Furthermore, cardiovascular risk factors, especially hypertension, are key factors for the prevention of CVD (the secondary stage of CVD prevention). To prevent CVD, it is important to improve lifestyle and reduce cardiovascular risk factors in the early stage. The health behaviors appearing in recent guidelines for the management of hypertension are also important for the primary prevention of stroke.

The guidelines put out by the United States,[7] Europe,[8] China,[9] and Japan[10] for lifestyle modifications for prevention of hypertension are similar, namely: (1) salt restriction, (2) high consumption of vegetables and fruits, (3) increased intake of fish and reduced content of saturated/total fat, (4) appropriate weight control, (5) regular physical exercise, (6) moderate alcohol consumption, and (7) quitting smoking. These factors are also considered as important stroke-prevention guidelines.[11,12]

In this review, I compare finding from studies on lifestyle status in Westerners and East Asians in relation to these basic hypertension guidelines (Table).

Salt Restriction

Many epidemiological studies have shown that reduced salt intake is directly related to decreased BP.[13–15] The Dietary Approaches to Stop Hypertension (DASH) diet, which was a randomized trial comparing the effects on BP of 3 total salt intake levels (8.3, 6.2, and 3.8 g/d for high, intermediate, and low salt intakes), showed significantly lower systolic (SBP, −5.9, −5.0, and −2.2 mm Hg) and diastolic BPs (DBP, −2.9, −2.5, and −1.0 mm Hg) at each salt level, respectively.[14] The DASH diet and salt reduction independently lowered SBP and DBP.

In a Chinese study that included a 7-day low-salt intervention (51.3 mmol/d), a 7-day high-salt intervention (307.8 mmol/d), and a 7-day high-salt plus potassium supplementation (60 mmol/d), the correlation coefficients of the SBP responses to low-sodium and high-sodium intervention were −0.47 and that to high-sodium intervention and potassium supplementation was −0.52.[16] These correlation coefficients were greater than those reported by the DASH-Sodium trial.[17]

The Intersalt Study[13] and the INTERMAP (International Study of Macro-/Micronutrients and Blood Pressure) Study[18] reported medium values of urinary salt excretion of 5.9 to 8.0 and 8.3 to 10.7 g/d in the United States, 8.8 and 7.5 to 9.4 g/d in the United Kingdom, 11.5 to 14.2 and 14.6 to 17.2 g/d in Northern China, 9.2 and 7.5 to 8.8 g/d in Southern China, and 10.2 to 11.8 and 10.9 to 12.3 g/d in Japan, respectively. Salt intake by East Asians is higher than that by Westerners. This tendency was more remarkable 50 years ago. Dahl[19] showed a positive linear relationship between the prevalence of hypertension and mean salt intake across 5 population groups in the 1950s: 4 g/d among Alaskan Eskimos, 7 g/d in Marshall Islanders (Pacific Ocean), 10 g/d in the United States (Brookhaven), 14 g/d in Hiroshima (South Japan), and 27 g/d in Akita (Northeast Japan). Dahl[19] also noted a strong north–south trend in death rates of stroke in Japan.

The salt intake of North Japan is among the highest in East Asia. This extremely high sodium intake is attributable to higher consumption of tsukemono (Japanese pickles), soy sauce (seasoning), and miso soup. Higher carbohydrate intake (rice) and lower saturated fat and animal protein intakes (meat) are also observed in North Japan. These dietary patterns do not maintain adequate arterial walls and may lead to intracerebral hemorrhage.[20]

Asians are likely to have a genetically high salt sensitivity.[21,22] The Gly460Trp variant of the *α-adducin* gene has been associated with renal sodium retention and salt-sensitive hypertension through enhancement of the activity of the

Received May 1, 2013; first decision May 16, 2013; revision accepted December 15, 2013.

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(*Hypertension*. 2014;63:00-00.)

Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.113.00543

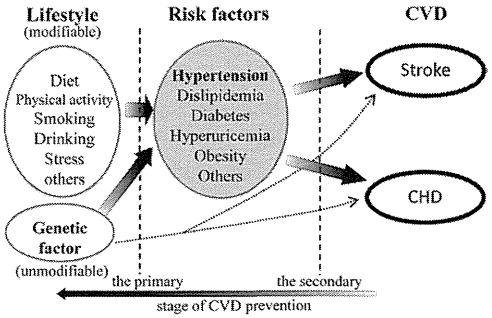

Figure. Schema of the progression from lifestyle changes to the incidence of hypertension and cardiovascular disease (CVD). CHD indicates coronary heart disease.

sodium pump. A meta-analysis showed a statistically significant association between salt sensitivity and α-*adducin* Gly460Trp polymorphism in Asians (odds ratio, 1.33; 95% confidence intervals [CIs], 1.06–1.69), but not in whites, indicating that the BP response to sodium varies among ethnic groups.[23] The frequencies of a common variant at codon 235 of the angiotensinogen gene with methionine-to-threonine amino acid substitution, the T235 allele of M235T, were 81% in Japanese[24] and 42% in whites.[25] The frequencies of the T(-344) allele of the T(-344)C polymorphism of the aldosterone synthase gene were 69% in Japanese[26] and 53% in whites.[27] The frequencies of the T825 allele of the C825T polymorphism for the G-protein β3 subunit were 52% in Japanese[28] and 25% in whites.[29]

High Consumption of Vegetables and Fruits

Dietary fiber, potassium, magnesium, and antioxidant vitamins are abundant in vegetables and fruits. In the Health Professionals Follow-Up Study, dietary fiber, potassium, and magnesium were inversely related to baseline SBP and DBP and to changes in BP during a 4-year follow-up among US men.[30] For men with a fiber intake of <12 g/d, the hazard ratio of hypertension was 1.57 (95% CIs, 1.20–2.05) compared with a fiber intake of >24 g/d. Fruit fiber but not vegetable or cereal fiber was inversely associated with incidence of hypertension.[30] On the contrary, the Nurses' Health Study has shown an inverse association between intakes of fruits and vegetables and SBP and DBP among 41 541 white US female nurses without diagnosed hypertension, cancer, or CVD.[31] Meanwhile, the Chicago Western Electric Study demonstrated that vegetable protein, total carbohydrate, β-carotene, and an antioxidant vitamin score based on vitamin C and β-carotene were inversely and significantly related to average annual change of SBP in men for an 8-year follow-up period.[32] During 7 years of follow-up, compared with the <0.5 cups/d group, the annual changes of SBP were −0.40 and −0.32 mm Hg for 0.5 to 1.5 cups/d of vegetables and fruits in men.[33] Therefore, diets higher in fruits and vegetables may reduce the risk of developing hypertension.

The Ohasama study has shown that higher intake of fruit is associated with a lower risk of future home hypertension.[34] During a 4-year follow-up, the highest quartile of fruit intake was associated with a significantly lower risk of future home

Table. Comparison Between Western and East Asian Studies According to the Lifestyle in the Hypertension Guidelines

Lifestyle Modification	Epidemiological Findings	Comparison Between Westerners and East Asians
Salt restriction	Reduced salt intake is related to decreasing BP.	Salt intake: Westerners<East Asians
		Salt sensitivity: Westerners<<East Asians
High consumption of vegetables and fruits	Diets higher in vegetables and fruits may reduce the risk of developing HT.	
Increased intake of fish, reduced content of saturated/total fat, and other type of diet		
Fish	Fish (n-3 PUFA) is a weak but significantly inversely associated with BP.	Westerners, Chinese<Japanese
Soy*	Soy intake reduces risk of CVD and may reduce BP. However, more evidence needs to accumulate.	Westerners, Chinese<Japanese
The DASH diet*†	Salt reduction lowered systolic and diastolic BP.	
The Mediterranean diet*	The Mediterranean diet associated with moderate but significant reduction of systolic and diastolic BP.	
Appropriate weight control	Obesity and overweight are risk factors for CVD and HT.	Obesity: Westerners>>East Asians
Regular physical exercise	Physical inactivity is a risk factor of HT.	
Moderate alcohol consumption	Excessive drinking is a risk factor for increased BP.	Drinking rate: Westerners<Japanese (men), Westerners>East Asians (women)
		ALDH deficient: Westerners<<East Asians
Quitting smoking		Smoking rate: Westerners<East Asians
		Population-attributable fraction for CVD: Westerners<East Asians (men)

ALDH indicates aldehyde dehydrogenase; BP, blood pressure; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; HT, hypertension; and PUFA, polyunsaturated fatty acid.

*Appeared in 2013 European Society of Hypertension/European Society of Cardiology Guidelines.[8]

†Appeared in Seventh report of the Joint National Committee.[7]

< indicates less than; >, greater than; <<, much less than; and >>, much greater than.

hypertension (odds ratio, 0.40; 95% CIs, 0.22–0.74). However, there was no association between higher vegetable intake and future home hypertension. The Shibata study demonstrated that serum vitamin C concentration was inversely associated not only with SBP and DBP, but also with incident stroke (*P* for trend=0.017).[35] These studies suggest that a plant-based dietary pattern including fruits and vegetables benefits BP control in both Western and East Asian countries.

Increased Intake of Fish, Reduced Content of Saturated/Total Fat, and Other Types of Diet

Epidemiological studies show that dietary n-3 polyunsaturated fatty acids (PUFAs) and fish oil had a weak but significantly inverse association with BP.[36,37] Even a small amount of fish intake (30–60 g/d) reduces the risk of CHD and sudden cardiac death in Western countries.[38] In a large cohort study, a high consumption of fish (180 g/d) was associated with an ≈40% reduced risk of CHD, compared with low fish consumption (<23 g/d).[39] This means that higher intake of fish can further reduce the risk of initial CHD events. The WHO-CARDIAC (WHO Cardiovascular Diseases and Alimentary Comparison) Study revealed an inverse relationship between the age-adjusted CHD mortality rate and the plasma levels of n-3 PUFAs worldwide.[40] East Asians had lower averages of saturated fatty acid than Westerners.[15] Mean dietary n-3 PUFAs in Japan is higher than those in Western countries and China.[15] Japanese have among the highest n-3 PUFA intakes and one of the lowest CHD mortalities worldwide. However, Japanese have higher salt intake and higher BP, counterbalancing their high fish intake.

As another significant characteristic of Japanese food, many studies on soy intake have reported that a higher dietary intake of soy reduced the risks of cardiovascular risk factors, notably on intermediate end points such as hyperlipidemia.[41] Higher soy and isoflavone intakes were associated with reduced risks of ischemic stroke and CHD in Japanese women. The risk reduction was accentuated for postmenopausal women.[42] The WHO-CARDIAC Study showed an inverse relationship between age-adjusted CHD mortality rate and 24-hour urinary isoflavone excretion in men worldwide. Japan and Taipei have some of the highest soy intakes and some of the lowest CHD mortality rates in men worldwide.[40] Both the higher fish intake and high soy intake among Japanese may contribute to its status as the country with the lowest CHD mortality worldwide. However, the evidence of association between soy and BP has been limited.[43]

The Mediterranean diet, with its higher contents of fruits, vegetables, legumes, nuts, cereals, fish, and olive oil, has been shown to be associated with a moderate, but significant, reduction of 3.1/1.9 mm Hg in SBP/DBP during a median 4.2-year follow-up.[44] These results are consistent with those of the DASH study.[16]

Appropriate Weight Control

Obesity and overweight have been rapidly increasing throughout the world in recent decades. The mean body mass index (BMI) levels (kilograms per meter squared) in men and women from East Asia (23.7 and 23.2 in Japan and 22.4 and 23.9 in China) are generally much lower than those of Westerners (27.7 and 27.2 in the United Kingdom and 29.1 and 28.7 in the United States).[15] Obesity and overweight are established risk factors for CVD, hypertension, dyslipidemia, diabetes mellitus, and metabolic syndrome.[45] The Framingham Heart Study showed that hypertension is approximately twice more prevalent in obese individuals than in nonobese individuals.[46] The study demonstrated that the highest quintile of the BMI group exhibited 16/9 mm Hg higher SBP/DBP than those in the lowest quintile (increase in 4 mm Hg SBP per 4.5 kg increased weight).[47] A meta-analysis of 25 studies has estimated that BP reductions were −1.05 mm Hg systolic and −0.92 mm Hg diastolic when expressed per kilogram of weight loss.[48]

In Japanese male office workers, BMI was shown to be a strong risk factor for incidence of hypertension in a 4-year follow-up.[49] Compared with BMI <18.5 kg/m^2, the hazard ratios of hypertension were 2.0, 2.3, and 2.3 for BMIs of 22.0 to 24.9, 25.0 to 25.9, and ≥30 kg/m^2, respectively. Weight gains (>2 kg) increased the risk of hypertension by 1.2 times.

Regular Physical Exercise

Many prospective cohort studies have demonstrated that physical inactivity is associated with an increasing risk of hypertension,[50–52] metabolic syndrome, diabetes mellitus,[53] CHD,[54] stroke,[51,54,55] cancer,[56] and all-cause mortality.[54,56] In a longitudinal study during 4-year follow-up in 1970, the relative risk for hypertension among the low-fitness group (72% of the group) was 1.5 times that of the high-fitness group.[57] Subjects who moved from the low-fitness to the high-fitness group during the follow-up period had approximately half the risk of developing hypertension compared with those whose fitness levels remained low.[57] In another study, normotensive subjects conducted cardiorespiratory fitness at the baseline, and each maximal metabolic equivalent unit was associated with a 19% lower risk (95% CIs, 12%–24%) during an 8.7-year follow-up period.[58]

In the Shibata study, heavy physical activity was a risk factor for incidence of stroke (hazard ratio, 3.3; 95% CIs, 1.2–9.5) during 1977 to 1992.[59] In the 1970s, most residents engaged in agricultural work, usually by hand, and had no exercise or sports. Although mechanization has gradually reduced their amount of physical labor, they still work much harder than urban or sedentary populations. In the Osaka Health Survey, in 59 784 person-years of follow-up, durations of subjects' walk to work of 11 to 20 and ≥21 minutes were associated with 0.88 and 0.71 times reduced risk of progressive hypertension (*P* for trend=0.02).[52]

In a meta-analytic study, the studies reviewed demonstrated a robust protective effect of active commuting on cardiovascular outcomes (hazard ratio, 0.89; 95% CIs, 0.81–0.98).[51] In another meta-analysis study using pedometers, 8 randomized controlled trials showed that pedometer users significantly increased their physical activity by 2491 steps/d more than controls.[50] Participants in this intervention significantly decreased their SBP by 3.8 mm Hg.

Moderate Alcohol Consumption

Alcohol consumption is higher in Japanese men (ethanol, 26.7 g/d) than in men in the United States (10.1 g/d) and United

Kingdom. (16.6 g/d). However, for women, consumption in Westerners is higher than in East Asians.[15] Nearly 50% of Koreans, Chinese, and Japanese are found to be aldehyde dehydrogenase (ALDH) deficient, the most frequent manifestation of which is called the Oriental flushing syndrome. ALDH deficiency is a risk factor for increased BP,[60] as is excessive drinking.[61] The high alcohol intake and high rate of ALDH deficiency among Japanese men may contribute to their elevated BP.

In a systematic review, an overall odds ratio for hypertension in 2*2 homozygotes of ALDH2 was 2.4 times higher than in wild-type homozygotes (*1*1).[62] This has turned out to be the case with a locus associated with BP-related traits that has recently been identified near the *ALDH2* gene at 12q24.13 in East Asians. Eight common single-nucleotide polymorphisms seem to identify a common ancestral haplotype (H3). Haplotype H4 is common in East Asians (frequency, 38%) but is absent in Europeans and is rare in Africans (4%).[63] Haplotype H5 is common in East Asians (29%) but is absent in Europeans and Africans. Haplotype H7 is common in Europeans (36%) but is absent in East Asians and Africans.

Quitting Smoking

Both normotensive and untreated hypertensive smokers present higher daily BP levels than nonsmokers.[64,65] Epidemiological data have shown that the smoking rates in East Asian men remain high at 40% to 60%, although this is after declining substantially for the past 20 years. The smoking rates were lower in East Asian women at 3% to 15% compared with Western women.[66] Another epidemiological study demonstrated that the prevalences of smoking in men were higher in East Asian (68% in South Korea, 63% in China, and 47% in Japan) region than in the Western Pacific region (16% in Australia and 26% in New Zealand).[67] The population-attributable fractions of CHD caused by smoking men and women were higher in the East Asian region (29% and 23% in South Korea, 27% and 22% in China, and 22% and 17% in Japan, respectively) than in the Western Pacific region (10% and 8% in Australia and 13% and 10% in New Zealand, respectively). Australia and New Zealand, with predominantly white populations, had relatively low smoking prevalences and therefore low population-attributable fractions for CVD. In a Japanese cohort study, the population-attributable fraction for CVD among men without metabolic syndrome who smoke (21.8%) was approximately the same as that among men with metabolic syndrome (19.4%).[68]

Conclusions and Perspectives

Appropriate lifestyle modifications are the first step of preventive hypertension. Official recommendations regarding lifestyle changes to improve hypertension are similar in East Asian and Western countries. However, the contributions of BP to stroke are different for Westerners and East Asians, attributable to differences in genetics and lifestyle. High consumption of fruits and vegetables, regular physical exercise, and maintaining appropriate body weight are all beneficial for BP control in both Western and East Asian populations. Fish and n-3 PUFA have a weak but significantly inverse association with BP. East Asians have the benefit of diets higher in fruits and vegetables and fish and less incidence of obesity. On the contrary, East Asians have a genetically higher salt sensitivity and a greater salt intake than Westerners. Excessive alcohol intake contributes to the increased BP in Japanese men, especially given their high rate of ALDH deficiency. The smoking rates in East Asian men are also higher than that in Western countries. To maintain an appropriate BP, East Asians should pay particular attention to quitting smoking and reducing salt and alcohol intake, whereas Westerners need to pay attention to weight control including regular exercise and consider replacing dietary meat high in saturated fat with fish. Further comprehensive prospective studies are anticipated to show how each factor contributes to BP control and a reduced risk of CVD in Westerners and East Asians.

Acknowledgments

We thank Drs Yuhei Kawano, Kei Kamide, and Yoshio Iwashima for their study discussion.

Sources of Funding

This study was supported by grants-in-aid from the Ministry of Health, Labor, and Welfare of Japan (H24-Junkankitou-011), the Intramural Research Fund of the National Cerebral and Cardiovascular Center (22-4-5), and by a grant (No. 25293147) from the Ministry of Education, Science, and Culture of Japan.

Disclosures

None.

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Uchiyama S, Amarenco P, Minematsu K, Wong KSL (eds): TIA as Acute Cerebrovascular Syndrome.
Front Neurol Neurosci. Basel, Karger, 2014, vol 33, pp 69–81 (DOI: 10.1159/000351892)

Epidemiology of Transient Ischemic Attack

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Abstract

Few epidemiologic data are available regarding the prevalence and incidence of transient ischemic attack (TIA). Here, the incidence of TIA and that of subsequent stroke events were reviewed. The incidences of TIA in Europe were 0.52–2.37 and 0.05–1.14 in men and women aged 55–64, 0.94–3.39 and 0.71–1.47 in those aged 65–74, and 3.04–7.20 and 2.18–6.06 in those aged 75–84, respectively. The corresponding incidences are similar in the United States, and lower in Japan. Higher incidences were revealed in men compared with women. The incidence of TIA increased very markedly with age, regardless of race or gender. The evidence of risk factors for TIA excluding ischemic strokes is very limited. The ABCD/ABCD^2 score was developed to predict individual risk and to triage patients on the first presentation. In prognostic TIA, the crude rate of stroke risks (%) for general populations were 1.7, 4.8, 6.6, 8.5, and 11.4 at 2 days, 1 week, 1 month, 3 and 6 months, whereas those for hospital patients were 13.7 and 12.4 at 1 and 3 months, respectively. There is very limited evidence of an association between a family history of stroke and the incidence of stroke after TIA, which showed that family history of stroke does not predict the risk of ischemic stroke after TIA. There is also limited evidence of seasonal variation in TIA incidence. TIAs were reported to be most frequent in autumn or spring and less common in winter or spring to summer, and most frequent on Mondays. There seems to be no consensus regarding seasonal differences in TIA incidence.

Transient ischemic attack (TIA) is an acute episode of temporary neurologic impairment lasting <24 h, caused by focal ischemia in the brain or retina. TIAs are variable in duration, commonly lasting from 5 to 60 min, but they occasionally last as long as 24 h, but may leave no persistent neurological deficit [1]. According

Table 1. Prevalence of TIA according to age, sex, and race/ethnic group

Population	Age, years	TIA, %		Year and reference
		men	women	
African-Americans				
Jackson, Miss., US				1996 [2]
	45–54	1.5	3.2	
	55–64	1.7	3.2	
	Total	1.6	3.2	
Forsyth, N.C., US				1996 [1]
	45–54	4.0	7.6	
	55–64	4.6	7.8	
	Total	4.3	7.7	
Evans, Ga., US				1973 [3]
	45–54	12.1	0.0	
	55–64	8.9	13.8	
	65	12.1	8.6	
European-Americans				
Forsyth, N.C., US				1996 [2]
	45–54	3.2	5.1	
	55–64	2.5	6.4	
	Total	2.9	5.7	
Evans, G.A., US				1973 [3]
	45–54	20.8	4.9	
	55–64	15.5	10.4	
	65	30.3	18.2	

to the recent American Heart Association/American Stroke Association diagnostic recommendations, TIA patients should undergo a neuroimaging evaluation within 24 h of symptom onset. Patients who have experienced a TIA are at high risk of stroke. However, there are few epidemiologic data on TIA, especially reviews of the incidence and prognostic value of TIAs. In this review, I will focus on the incidence of TIA and subsequent stroke events from an epidemiological point of view.

Prevalence and Incidence of Transient Ischemic Attack

The prevalence of TIA according to age, sex, and race/ethnic group is shown in table 1 [2, 3]. Among African-Americans, the prevalence of TIA does not seem to increase according to age in both men and women. According to the Atherosclerosis Risk in Communities (ARIC) Study, the prevalence of TIA in African-American

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men and women per 1,000 persons was 1.5–1.7 and around 3.2 in Jackson, Miss., but 4.0–4.6 and 7.6–7.8 in Forsyth, N.C., respectively [2]. However, in Evans County, Ga., the prevalence of TIA in the age groups 45–54, 55–64, and 65+ years was 12.1, 8.9, and 12.1 in men and 0, 13.8, and 8.6 in women per 1,000 persons, respectively [3]. These prevalence results are much higher than those obtained in Jackson and Forsyth. The data for Jackson and Forsyth are from 1996, which is 23 years after the Evans data. These two sets of data may not be compared simply because of a different generation.

In the ARIC study, the diagnosis of TIA was categorized as *definite* for a sudden onset of transient limb paralysis, with or without other signs, lasting up to 24 h and leaving no significant deficit; *probable* for other transient focal neurologic deficits lasting up to 24 h; *possible* for a less clear-cut history of symptoms or non-focal symptoms, or *vague* for anxiety and/or emotional symptoms. Evans County, is located in 'the Stroke Belt' in the south-eastern United States, which shows relatively higher stroke incidence. Therefore the prevalence of TIA in Evans County seems to be greater than in other areas.

In a European-American population in Forsyth, the prevalence of TIA was 2.9 and 5.7 in men and women per 1,000 persons, respectively. In Evans, the TIA prevalence of a European-American population was 20.8, 15.5, and 30.3 in men and 4.9, 10.4, and 18.2 in women per 1,000 persons according to the 45–54, 55–64, and 65 or older (65+) age groups, respectively. The prevalence of TIA tends to increase according to age in both men and women.

The Hisayama study examined the prevalence of TIA in the Japanese population [4]. The prevalence of TIA in the Hisayama study was 4.9 per 1,000 persons [4], less than half that in the European-American population in Evans. (13.8 per 1,000 persons) [3]. The etiology of incident TIA in Japan may be different from that in Western countries. Among the Hisayama participants with TIA, 11 subsequent cerebral infarctions were observed; they were diagnosed as 6 lacunar infarctions, 3 embolisms, and 2 atherothromboses by clinical and/or pathological finding or autopsy. The ARIC study showed that TIA due to atherosclerosis was attributable to myocardial infarction in 57% and to stroke in 38% of mortality patients (n = 37) [2]. TIAs due to atherosclerosis (which is usually of carotid artery origin) are estimated to be less common in Japan than in Western countries, and lacunar stroke might be important as an etiology of TIA in Japan [2].

As illustrated in figure 1 [4–11] and table 2, [4, 5, 7, 8, 10, 12–15] the Hisayama study found that the average incidence of the first TIA was 0.78 and 0.38 per 1,000 person-years in men and women, respectively [4]. According to community studies in the US, the average incidence rate for the first TIA was 0.31 per 1,000 person-years (0.93 per 1,000 person-years for those aged >65 years) in Rochester, Minn. [16], and 1.1 per 1,000 person-years in Seal Beach, Californian community [11], where the incidence of all strokes and TIA with previous cerebrovascular events were 7.1 and 1.4 per 1,000 person-years during the period 1963–1967, respectively.

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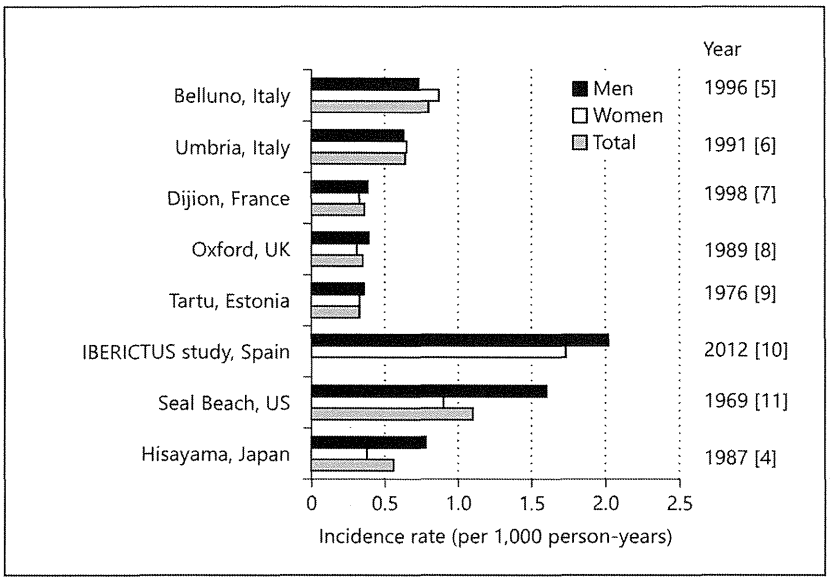

Fig. 1. Incidence of TIA in several countries.

The incidence for men was 9.7, 1.7 times the incidence of 5.7 for women per 1,000 person-years.

The incidence rate of TIA in Belluno, Italy, was 0.80 per 1,000 person-years, and the incidence was non-significantly higher in women than in men (0.73 per 1,000, 95% confidence interval, CI: 0.57–0.91 in men, and 0.87 per 1,000, 95% CI: 0.70–1.06 in women) [5]. After adjustment for the European population, the overall incidence rate decreased to 0.58 per 1,000 inhabitants per year. The mean age of new TIA patients was 73.9 years, and the women were significantly older than the men ($p < 0.001$). The SEPIVAC study of a population in Umbria, Italy revealed a crude rate of 0.64 per 1,000 per year (95% CI: 0.52–0.78), and the authors reported that the rate adjusted to the European population is 0.42 (95% CI: 0.33–0.54) [6]. It is of note that in the Umbria population, one third of the new TIA patients was cared for at home [6]. In Tartu, Estonia, USSR, from 1970 to 1973, the incidence of TIA was 0.33 per 1,000 person-years [9], and the mortality rate for stroke for this population was 0.98 per 1,000 person-years [9]. The Italian and Estonian data on the incidence of TIA, its dependence on age and sex, and mortality rate are close to the corresponding data reported from other countries.

The Oxfordshire Community Stroke Project showed that the crude TIA incidence rate and the TIA rate standardized to the 1981 population of England and Wales were 0.35 and 0.42 per 1,000 person-years, respectively [8]. The incidence of TIA increased sharply with increasing age, and the overall incidence in men was very similar to that

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Table 2. Incidence and mortality of TIA according to age, sex, and race/ethnic group (per 1,000 person-years)

a Asia: Hisayama, Japan

Age group	Incidence		
	men	women	total
40–49 years	0.41	0.00	0.18
50–59 years	1.16	0.57	0.84
60–69 years	0.89	0.52	0.69
70– years	0.45	0.66	0.66
Total	0.78	0.38	0.56

b Europe

Age group	Incidence			Mortality		
	men	women	total	men	women	total
Udine District, Italy [5], 2007–2009						
<45 years	0.03	0.01	0.02			
45–54 years	0.29	0.05	0.16			
55–64 years	0.52	0.05	0.26			
65–74 years	0.94	0.71	0.81			
75–84 years	3.93	2.51	3.04			
85– years	5.34	3.44	3.95			
Total	0.56	0.49	0.52			
IBERICTUS, Spain [7]						
18–24 years	0.03	0.03	0.03	0.00	0.00	0.00
25–34 years	0.08	0.09	0.08	0.00	0.00	0.00
35–44 years	0.35	0.22	0.29	0.06	0.03	0.05
45–54 years	0.96	0.36	0.66	0.07	0.13	0.09
55–64 years	2.37	1.14	1.75	0.10	0.10	0.10
65–74 years	4.91	2.58	3.67	0.06	0.12	0.09
75–84 years	10.13	6.93	8.27	0.13	0.08	0.10
85– years	14.45	13.60	13.88	0.22	0.20	0.02
Total	2.02	1.73	1.87	0.11	0.12	0.12
Central Spain (the NEDICES study) [7]						
65–69 years	9.47	3.29	6.06			
70–74 years	11.27	15.25	13.49			
75–79 years	22.33	18.02	19.83			
80–84 years	10.75	15.22	13.53			
85– years	30.61	21.47	24.90			
Total	14.30	12.83	13.45			
Belluno, Italy [8]						
0–54 years	0.06	0.01	0.03			
55–64 years	1.09	1.04	1.06			
65–74 years	3.39	1.47	2.24			
75–84 years	7.20	6.06	6.39			
85– years	7.57	10.54	10.06			
Total	0.73	0.87	0.80			

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